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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,041	08/15/2000	W. Michael Kavanaugh	1615.002/200130.503	2270

27476 7590 07/14/2003

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/640,041	Applicant(s) KAVANAUGH ET AL.	
	Examiner Michail A Belyavskyi	Art Unit 1644	

-- Th MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *10-13 and 15-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/28/03 has been entered.

Claims 1-37 are pending.

Claims 10-13 and 15-37 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention.

Claims 1-9 and 14 wherein the isolated nucleotide nucleic acid molecule comprising a polynucleotide which encodes SEQ ID NO: 4 and the nucleic molecule is SEQ ID NO: 3 are under consideration in the instant application.

In view of the amendment, filed 04/28/03 (Paper No. 22), the following rejections remain:

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 3 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, Paper NO: 15, mailed on 08/27/02. *This is a New Matter rejection*:

Claim 3 now claimed an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having an amino acid sequence from 1 to 115 or from 2 to 115 of SEQ ID NO:4 wherein said polypeptide has at least one conservative amino acid substitution and at least 90 % identity with SEQ ID NO:4 and mitogenic activity as determined by *Xenopus* oocyte maturation assay which represents a departure from the specification and claims as originally filed because specification and claims as originally filed do not provide a clear support for isolated nuclear acid molecule comprising all recited properties.

Applicant's arguments, filed 04/28/03 (Paper No. 22), have been fully considered, but have not been found convincing.

Applicant asserts that the polynucleotides of the invention are disclosed at least on page 2, lines 1-15 and lines 19-26 and page 10, lines 13-24 and that the mitogenic activity is disclosed at page 38, lines 15-23.

Contrary to Applicants assertion, the issue raised by the examiner was not how to determine the mitogenic activity by *Xenopus* oocyte maturation assay but rather that the passages pointed by the applicant do not provide a clear support for an isolated nucleic acid with all recited properties, i.e. comprising a polynucleotide encoding a polypeptide having an amino acid sequence from 1 to 115 or from 2 to 115 of SEQ ID NO:4 wherein said polypeptide has at least one conservative amino acid substitution and at least 90 % identity with SEQ ID NO:4 and mitogenic activity.

4. Claims 1-9 and 14 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: 1) an isolated nucleic acid molecule comprising a polynucleotide selected from the group recited in claim 1 (a) – (c); 2 an isolated nucleic acid molecule comprising 345 contiguous nucleotides of SEQ ID NO:3, as recited in claim 2 ; a method of making a recombinant vector comprising inserting a nucleic acid molecule of claim 1 (a) –(c), and said recombinant vectors and a method of making a recombinant host cell comprising introducing said recombinant vectors, a recombinant host cell thereof and a method of producing a polypeptide comprising culturing said host cells as recited in claims 5-9 does not reasonably provide enablement for: A) *any* isolated nucleic acid molecule comprising a polynucleotide recited in claim 1 (d); B) *any* isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having amino acid sequence from 1 to 115 of SEQ ID NO:4, or from about 2 to about 115 of SEQ ID NO:4, wherein said polypeptide has at least one conservative amino acid substitution and at least 90 % identity with SEQ ID NO:4 , as recited in claim 3; D) any composition comprising an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO: 4 or at least 90 % identical to a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO:4 as recited in claim 14 for the same reasons set forth in the previous Office Action, Paper NO: 15, mailed on 08/27/02.

It is also noted that the terms "comprising" is an open-ended and expand isolated nucleic acid molecule comprising an amino acid sequence from 4 to 50 of SEQ ID NO:4 or at least 90 % identical to a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO:4 as recited in claim 14, to include additional non disclosed amino acid sequences .

Applicant's arguments, filed 04/28/03 (Paper No. 22), have been fully considered, but have not been found convincing.

Applicant asserts that one of skill in the art is able to make and use a polynucleotide wherein the amino acid sequence at least 90 % identical with SEQ ID NO: 4 and has mitogenic activity as determined by Xenopus oocyte maturation. Applicant also asserts that further support for enablement comes from the Declaration under 37 C.F.R. 132 by Dr. Judith Abraham.

Contrary to Applicant's assertions, the issue raised by the examiner was that the specification fails to provide sufficient guidance as to which core structure of SEQ ID NO: 4 is essential for maintain its mitogenic activity and which changes can be made in the structure of SEQ ID NO: 4 and still maintained the same function.

The declaration by Dr. Judith Abraham only stated that there are several routine assays to determine biological activity of EGFH2. The issue raised by the Examiner was not how to determine biological activity of EGFH2 but rather that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected how to make : A) *any* isolated nucleic acid molecule comprising a polynucleotide recited in claim 1 (d); B) *any* isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having amino acid sequence from 1 to 115 of SEQ ID NO:4, or from about 2 to about 115 of SEQ ID NO:4, wherein said polypeptide has at least one conservative amino acid substitution and at least 90 % identity with SEQ ID NO:4 , as recited in claim 3; D) any composition comprising an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO: 4 or at least 90 % identical to a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO:4 as recited in claim 14.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated A) *any* isolated nucleic acid molecule comprising a polynucleotide recited in claim 1 (d); B) *any* isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having amino acid sequence from 1 to 115 of SEQ ID NO:4, or from about 2 to about 115 of SEQ ID NO:4, wherein said polypeptide has at least one conservative amino acid substitution and at least 90 % identity with SEQ ID NO:4 , as recited in claim 3; D) any composition comprising an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO: 4 or at least 90 % identical to a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO:4 as recited in claim 14 encompassed by the claimed invention other than "nucleic acids set forth by SEQ ID NO: 3" would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard

to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of EGFH2, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, making changes up to 10% of a polynucleotide sequences does not provide that the encoded protein will retain the same mitogenic activity as the unmutated polynucleotide.

Protein chemistry is probably one of the most unpredictable areas of biotechnology . It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular). Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Because of the lack of sufficient guidance and predictability in determining which nucleic acid sequences encode EGFH2 structures and would lead to functional EGF2 proteins with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to make claimed : A) *any* isolated nucleic acid molecule comprising a polynucleotide recited in claim 1 (d); B) *any* isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having amino acid sequence from 1 to 115 of SEQ ID NO:4, or from about 2 to about 115 of SEQ ID NO:4, wherein said polypeptide has at least one conservative amino acid substitution and at least 90 % identity with SEQ ID NO:4 , as recited in claim 3; D) any composition comprising an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO: 4 or at least 90 % identical to a polypeptide comprising an amino acid sequence from 4 to 50 of SEQ ID NO:4 as recited in claim 14 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. No claim is allowed

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Patent Examiner
Technology Center 1600
July 14, 2003

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